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Mechanisms of Peripheral Nerve Injury – What to Treat, When to Treat

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1. Introduction

Peripheral nerve injury, sometimes referred to as acquired nerve injury, is a catastrophic injury that imposes a number of negative outcomes that usually inflict one or more adverse health conditions or disabilities on its victims. These adverse health conditions and disabilities frequently place both short-term and long-term burdens on individuals, families, communities, the workplace, the health care system and economies in general. Considerable money and effort have been expended on attempts to lessen, prevent or ameliorate the effects of trauma on peripheral nerves.

There are many outcomes of neuropathy of peripheral nerves. Neuropathic pain is perhaps the best documented, largely because of the enormous impact of chronic neuropathic pain on individuals and the fact that it tends to be refractory to medical treatment [1, 2]. However, other outcomes of secondary injury to peripheral nerves include, in terms of sensory disturbance, numbness, dysesthesia (an unpleasant abnormal sensation, whether spontaneous or evoked), paresthesia (an abnormal sensation, such as tingling, whether spontaneous or evoked), hypoesthesia (decreased sensitivity to stimulation, excluding the special senses) and loss of proprioception (possibly contributing to altered gait and to falls). In terms of motor control, peripheral neuropathy can lead to weakness, loss of movement, loss of corrective motor control and loss of muscle mass. Neuropathy of the autonomic nervous system can be manifest as orthostatic hypotension, dysautonomia, altered sudomotor function, and the like. Injury or damage to nerves or nerve cells can be the result of factors or events that are unanticipated or unexpected, such as an accident, while other factors or events can be anticipated, such as a result of chemotherapy or even surgical intervention.

It is the thesis of the present overview that many of the negative outcomes and disabilities of peripheral nerve injury can be reduced in severity, or prevented altogether, by early interven-

tion with the appropriate methods, procedures and pharmaceutical formulations, continued for a medically-beneficial period of time.

While there are currently practices and interventions to treat, manage or diminish the negative outcomes of peripheral nerve injury once they have been established, immediate or early preventive approaches targeted at the development phase of these outcomes are nonexistent, few or ineffective. That is, at the time of a traumatic event medical attention focuses on treatment of immediate symptoms such as bleeding or to avoid infection, but medical attention does not typically address treatment to prevent the cascade of restorative, or adaptive, and degenerative, or maladaptive, metabolic and biochemical processes that result from peripheral nerve injury and that lead to prolonged or permanent adverse health conditions and disability.

Peripheral nerve injury or damage is not only to nerves or nerve cells, but can include damage to neural support cells, such as satellite cells and myelin cells, and also local circulation. In the context of the present overview the term "neural support cell" is any cell that supports or could be considered to support the health, normal function and survival of nerves and nerve cells, and include myelin cells and satellite cells, astroglia, oligodendrocytes, Schwann cells, vascular endothelial cells, and the like. Further, the term "neural support tissue" is any tissue that supports or could be considered to support the health, normal function, phenotype, gene expression or survival of nerves, nerve cells or support cells, and include the vasculature or microvasculature, particularly the endothelial cells that prevent blood from leaking into peripheral nerve tissue and that provide the selective blood-nerve barrier that allows the passage of certain supportive chemicals into nerve tissue as well as the passage of nerve tissue wastes out of nerve tissue.

Degeneration of axons or of neural support cells triggers a cascade of activated chemical pathways that lead to injury to otherwise intact nerve cells, Schwann cells, local vasculature and even more remote nerve cells by entry of degradation products into the blood circulation.

Trauma can be of many different types. For example, physical trauma can occur in vehicle accidents, in workplace accidents, sports accidents, on the battlefield, from falls, from assaults, from landmines and from explosive or other blasts, and the like, but can also occur as a result of surgical or other medical procedures.

Chemical trauma to nerves or nerve cells or neural support cells or neural support tissues can occur, from alcohol overdose, drug abuse, stimulant drugs such as pentylentetrazol, carbon dioxide poisoning, acrylamide and related chemicals, overexposure to certain environmental chemicals such as copper or natural hazards such as scorpion venom toxin, herbicides, agricultural insecticides such as lindane, many industrial chemicals, neurotoxin bioterrorism chemicals such as soman and sarin, as well as radiation bioterrorism chemicals such as polonium and strontium.

Medically-induced trauma to nerves or nerve cells or neural support cells or neural support tissues can occur as a result of surgery, amputation, injections, laparoscopy, implants, during a medical procedure that reduces or impedes the blood supply to any tissue containing nerve cells for any period of time as described herein, chemotherapy (for example from methotrexate,

cisplatin, cytosine arabinose, carmustine, thiotepa among others), radiation therapy, immunosuppressants (such as tacrolimus).

Surgery in and of itself can produce other types of trauma that are injurious to nerves, nerve cells and nerve support cells and neural support tissues. For example, the life-saving benefits of cardiac surgery are frequently followed by manifestations of damage to peripheral nerves and chronic neuropathic pain, which remains a significant complication of cardiac surgery and occurs with an incidence of 15% [3]. In a ten-year overview it was reported that chronic post-surgical pain constitutes a significant medical need that may be amenable to be reduced or prevented [4]. The incidence of persisting pain following amputation is 50-85%, that of intrathoracic surgery is 30-55%, mastectomy is 20-50%. Persisting pain after even simple procedures such as hernia repair and cholecystectomy are reported to be 5-35% and 5-50%, respectively. Post-sternectomy pain has been reported to be as high as 28% [5], hysterectomy as high as 32% [6], caesarean section as high as 12-18% [7, 8]. These are all astounding numbers, especially given the position taken here that the persisting pain may be reduced or prevented by appropriate and timely pharmaceutical intervention.

Similarly to medical surgical procedures, the incidence of peripheral nerve injury resulting from medical chemotherapy procedures has been underappreciated. A recent systematic review [9] has calculated that the prevalence of patients with neuropathic pain as a result of chemotherapy varies between 19% and 39%. Neuropathology-inducing chemotherapy drugs include paclitaxel, bortezomib, ixabepiline and oxaliplatin, as examples.

Broader than chemotherapy, peripheral neuropathy resulting from medications and toxic chemicals may also be preventable. Drugs that can trigger peripheral neuropathy include some antibiotics, as well as drugs for other disorders, including infliximab, etanercept, leflunomide, linezolid, statins, dichloroacetate and others [10-12]. A number of industrial chemicals also have the potential to induce peripheral neuropathy [12, 13]. Based on available knowledge, these types of peripheral neuropathy can be reduced or prevented if the appropriate medical intervention is applied early.

2. Secondary injury resulting from peripheral nerve trauma

Peripheral nerve injury generally consists of two related processes, the initial injury and a secondary injury [14] that results from cascades of self-propagating metabolic and biochemical processes that lead to loss of cell function and cell death. Disability occurs to a large extent from the secondary injury that is triggered by the primary injury. Whether the numbers are large, as in the case of battlefield peripheral nerve injury, or small, as with falls in the elderly, peripheral nerve injury can be devastating to the individual. Whether the numbers are large, as those resulting from car accidents, or small, such as those resulting from laparoscopic surgery, the result of peripheral nerve injury can be a future of constant burning, debilitating neuropathic pain and other adverse health conditions.

In the context of the present overview the term "secondary injury" or "secondary damage", terms that can be used interchangeably for the present context, means any damage, injury,

harm, loss, change in structure, change in phenotype, change in gene expression or change in function or survival of nerves, nerve cells, neural support cells or neural support tissue that occurs after a traumatic event and develops over the seconds, minutes, hours, days, weeks or even months following such an event. Secondary injury or secondary damage is usually considered to result from consecutive or parallel biochemical cascades of cellular and metabolic processes that are activated or triggered by the trauma-induced direct tissue damage to a peripheral nerve. Secondary injury or secondary damage is usually considered to involve endogenous processes or biosynthetic pathways that govern, regulate or influence the structure, health, function, gene expression or survival of nerves or nerve cells, or cells or tissues upon which nerves or nerve cells depend to maintain health and function, such as neural support cells and neural support tissues often with delayed clinical presentation [14]. Whereas a primary injury is irreversible [15], this secondary injury is salvageable [14]. This secondary injury is a neuropathology that can be reduced or prevented by appropriate and timely intervention.

3. Functional outcomes of peripheral nerve injury

Neuropathic pain is defined as pain caused by damage, lesion, disease or altered function of the peripheral somatosensory nervous system and is characterized as a constant burning pain accompanied by hyperesthesia (increased sensitivity to stimulation, excluding the special senses). Hyperesthesia is usually clarified in clinical use as either hyperalgesia (increased pain from a stimulus that normally provokes pain) or allodynia (pain due to a stimulus that does not normally provoke pain). Neuropathic pain may also include periodic attacks of pain that feel like electric shocks or shooting pain.

In understanding mechanisms of peripheral neuropathic pain it is important to distinguish this type of pain from nociceptive pain and inflammatory pain. Nociceptive pain is pain that arises from actual or potential damage to non-neural tissue and is due to the activation of nociceptors in these tissues. Nociceptive pain functions to protect from potential tissue damage or from further tissue damage, and triggers physiological and behavioural reflexes to avert damage. Inflammatory pain is pain that is triggered by inflammation and serves to aid in healing and repair of injured non-neural tissue. Each of nociceptive and inflammatory pain is brought about by a specific set of mechanisms and each has a specific treatment algorithm. Neuropathic pain is different, not only with respect to underlying mechanisms and treatments [16], but it is considered to be a maladaptive pain, as this type of pain neither protects nor supports healing and repair.

4. Processes and mechanisms leading to peripheral neuropathology following peripheral nerve trauma

Trauma to a peripheral nerve has effects on sensory neurons, on motor neurons controlling skeletal muscle and on autonomic efferent neurons controlling the cardiovascular system and

organs. This accounts for the range of outcomes of peripheral nerve trauma indicated above. As much of the research in this area is focussed on symptoms, available knowledge tends to be clearly fractionated into the bases of sensory loss, motor loss or autonomic dysfunction.

The overriding research on sensory loss pertains to peripheral neuropathic pain, which will be surveyed here to exemplify the pathophysiological changes that occur in peripheral nerves more generally. Even here, though, much attention is focused on changes in the central nervous system [17], particularly at the level of the first sensory synapse in the spinal cord and in the brain stem [18, 19]. As a result, treatment options tend to focus on targets within the central nervous system [20-22]. Research also tends to focus on the incidence of neuropathic pain rather than on underlying neuropathological processes [18]. Notwithstanding this orientation, the first step here will be to examine the changes in peripheral nerves that result from injury.

Understanding pathophysiology arising from peripheral nerve trauma is further complicated by the various types of trauma, which consist largely of a total cut of a peripheral nerve, a partial cut, an event-triggered compression, a slowly-developing compression (such as from a tumour), and a degeneration of nerve cells or of neural support cells and neural support tissues. Total and partial cuts as well as event-triggered compression can occur as a result of an accident, a violent act or surgery. Degeneration can be induced, for example, by chemotherapy. Physical, surgical and chemical events provide a start time for medical care [4, 12, 23]. As post-herpetic neuralgia is associated with a time-locked event, which is the start of the symptoms of shingles, this type of neuropathic pain is included in this overview [24-26], as would be any other infection-or inflammation-induced neuropathy that is time-locked.

Multiple pathophysiological, neurochemical, and anatomical changes are triggered by peripheral nerve injury, whereby a simple focal peripheral nerve injury unleashes a range of peripheral as well as central nervous system processes that contribute to persistent pain and abnormal sensation. Repair mechanisms of neural tissues in response to injury, and the reaction of adjacent tissues to injury lead to a state of hyperexcitability in primary afferent nociceptors [27], a phenomenon termed peripheral sensitization. In turn, central neurons innervated by such nociceptors undergo dramatic functional changes including a state of hyperexcitability termed central sensitization [28].

Normally these sensitization phenomena extinguish as the tissue heals and inflammation subsides. However, when primary afferent function is altered in an enduring way by injury or disease of the peripheral nerves, these processes persist, become chronic and may be highly resistant to treatment.

Much of what has been learned regarding the pathophysiology of injury causing neuropathic pain has come from animal studies. Human laboratory studies, although limited in number, support the idea that the pathophysiological mechanisms discovered in animal models are valuable and relevant to our understanding of human neuropathic pain [29, 30]. There are several animal models of peripheral neuropathic pain, largely based on the types of primary injury or trauma that lead to peripheral neuropathic pain in humans [31-39].

Effects of peripheral nerve injury in these models include major changes in the properties of nerve cells and their support cells, particularly the Schwann cells. Changes in sensory nerve

cells include spontaneous ectopic action potential generation, persisting sensitization of sensory nerve cell peripheral terminals, and increased release of excitatory neurotransmitters from their central nerve terminals [27, 40-42]. Other changes in sensory nerve cells include a change in function [43], changes in the expression of cell constituents such as sodium channels [44] and changes in the expression of neurotransmitters [45, 46], including *de novo* expression of substance P in large fibre, non-nociceptive sensory neurons [40]. While there is currently no universally effective treatment for peripheral neuropathic pain, one that is included in the algorithm of treatment regimens is gabapentin [16, 21], which is thought to act by reducing the release of excitatory neurotransmitters from the central terminals of sensory neurons [47, 48]; this action is thought to occur through inhibition of the influx of calcium into the nerve terminals, which is necessary for synaptic release mechanisms [49].

Two major hypotheses have been put forward to explain the role of sensory neurons in the generation of neuropathic pain [27]. One is the classic “excitable nociceptor hypothesis”, which implicates a reduced response threshold in nociceptive small C-fibre sensory neurons. Another hypothesis suggests ectopic impulse activity is generated in low threshold mechanoreceptor large fibre A β sensory neurons and that this activity is abnormally “amplified” in the spinal cord by central sensitization [27, 50]. The hypothesis implicating C-fibre sensory neurons in causing neuropathic pain is mainly based on the abnormal spontaneous activity observed in these neurons. However, several studies have shown that large fibre sensory neurons undergo significant changes in their electrophysiological properties as well as other phenotypic changes, such as the expression of substance P [51-53]. Further studies have shown that large fibre A β neurons, not the small C-fibre sensory neurons might be the major drivers of stimulus-evoked neuropathic pain and tactile allodynia [54].

Irrespective of these outcomes of peripheral nerve injury, which manifest in established neuropathic pain, the focus of the present overview is on the mechanisms and processes that lead to these outcomes. A consensus is that once these processes are set in place the resulting neuropathic pain is relatively refractory to medical treatment. The present overview therefore addresses the initial changes in peripheral nerve cells, neural support cells and neural support tissues that lead to long-term or permanent pathology, adverse health outcomes or disability.

5. Triggering events and cellular processes leading to adverse outcomes

Specific mechanisms triggered by injury to sensory nerve cells vary depending on the site of the trauma and the type of trauma [55]. There is also a reported difference in the restorative and degenerative processes activated between immature and mature rat models [56].

A cut to an axon induces an immediate influx of calcium, which disrupts the ionic balance of the nerve cell and initiates transport of a number of intracellular and extracellular chemicals to the nerve cell body in the dorsal root ganglion [57], contributing to spontaneous ectopic activity in small diameter normally nociceptive neurons and/or in the large diameter normally non-nociceptive neurons (summarized in [18, 27, 58]). Other changes are also induced in nerve

cell bodies in the dorsal root ganglia when injury occurs to the axons, including chromatolysis, displacement of the cell nucleus, cell shrinkage and a decrease in axonal transport [59].

Abrupt non-cutting trauma can also cause injury to axons, which then begin to degenerate over the next several days [60, 61], leading to cell death in a delayed, progressive process [62]. Degeneration of the central and peripheral terminal projections of the damaged and dying nerve cells leads to sprouting of the terminal projections of neighbouring undamaged nerve cells, constituting a morphological reorganization of the spinal cord neuronal circuitry [63] and perhaps also of the peripheral innervations of tissues.

Trauma to the axon also alters the normal flow of proteins orthogradely toward the cell body in the dorsal root ganglion, and retrogradely toward the peripheral terminal along intracellular filaments. This alters the information arriving to the protein assembly mechanisms in the cell body and this leads to changes gene expression of proteins. Changes in gene expression follow a temporally specific pattern [64], indicating that different cellular contents are produced at varying times following trauma to a peripheral nerve. In addition to changes in the expression of proteins there are also changes in the cellular distribution of these proteins, particularly of sodium and calcium channels [65], which are critically involved in neuronal excitability and conduction. Changes in gene expression and generation of specific proteins are particularly relevant to secondary injury including changes in the expression of neurotransmitters, such as substance P, of trophic factors such as brain-derived neurotrophic factor and other factors, as well as kinases and other degradative enzymes [45, 66].

Changes in expression and distribution of calcium channels have received particular attention. Expression of the α -2- δ subunit of voltage-gated calcium channels is increased in neuropathic pain models and this increase correlates with the onset and duration of pain scores [67]. The anticonvulsant, gabapentin, and its derivative, pregabalin, are both reported to bind to the α -2- δ subunit of voltage-gated calcium channels and inhibit transport of this subunit to nerve terminals [68]. Gabapentin and pregabalin have both shown clinical efficacy for treating chronic neuropathic pain in humans [16, 69, 70].

Changes also occur in Schwann cells. Any changes in the supporting Schwann cells are important to understand because of their pivotal role in sustaining the physiological properties of peripheral nerve cells and because they are involved in a degenerative process termed 'Wallerian degeneration' [71]. Schwann cells are the glial cells of the peripheral nervous system, and include myelinating cells and non-myelinating satellite cells. Dysfunction of Schwann cells is at the basis of several peripheral nerve disorders, such as Guillain-Barré disease and Charcot-Marie-Tooth disease [72-74]. As the Schwann cells decompose so do the myelin sheaths. The products of this decomposition trigger proliferation of new undifferentiated Schwann cells that align along the Bungner's bands that constitute the tubes within which the nerve bundles are contained, along with their support cells. Toll-like receptors are strongly induced by axotomy, they are critically involved in degeneration [75,76] and they lie at the crossroads of peripheral nerve pathology and pain [77].

Changes also occur in other non-neuronal cells, affected by axonal degeneration and Wallerian degeneration of axons. Macrophages and lymphocytes as well as immune cells from the blood infiltrate dorsal root ganglion cells and are attracted to the site of nerve damage [71, 78]. This

chemical milieu contains many components that impact on all cell types, including neurotrophic factors such as brain-derived neurotrophic factor, glial-derived neurotrophic factor, nerve growth factor and neurotrophin-3 [79-82], pro- and anti-inflammatory cytokines such as tumor necrosis factor (TNF- α), interleukin-1 α (IL-1 α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-10 (IL-10) and leukemia inhibitory factor [83, 84] and the chemokine monocyte chemoattractant protein-1 [85]. Axon-promoting chemicals are thought to provide support for regrowing axons [83]. Some components are thought to cause increased excitability of undamaged axons as a cause of neuropathic pain [86]. Even cutting ventral roots has been shown to lead to neuropathic pain behaviour in rats [87], presumably due to the migration of chemicals from degenerating nerve and neural support cells associated with motor control to intact neighbouring sensory neurons [88-90].

Peripheral nerves travel alongside blood vessels and trauma to the nerve often physically disrupts the blood-nerve barrier, allowing the milieu of chemicals produced by axon and Schwann cell degeneration to enter the bloodstream, which then carries these chemicals to remote parts of the body, including direct access to uninjured dorsal root ganglia, the enteric nervous system and the central nervous system [91]. This tends to carry peripheral nerve injury to remote sites beyond the site of a primary injury.

6. Processes and mechanisms of the changes in spinal cord resulting from peripheral nerve injury

Although the focus of the present overview is on peripheral nerve injury, changes in sensory nerve cells produce changes in spinal cord nerve cells, glial cells and other neural support cells, and it is generally held that some of the outcomes of peripheral nerve injury may be brought about as a result of changes in the spinal cord. For example, peripheral nerve injury produces excessive excitation and activation of sensory neurons, which causes excessive release of glutamate, substance P and other neurotransmitters from their central terminals in the spinal cord and brain stem. Besides leading to central sensitization, released neuropeptides regulate gene expression and therefore the phenotype of neurons in the spinal cord and brain stem [92]. Outcomes of peripheral nerve injury in animal models have been reported to include major changes in the properties of spinal neurons and spinal neural support cells and neural support tissues [93-95]. Peripheral nerve injury has also been reported to produce changes in the processing of sensory information at the spinal and supraspinal levels [96-101].

As a result of acute peripheral nerve injury, discharge from both damaged and adjacent intact primary afferent fibres becomes abnormal. This modified afferent drive in turn has been reported to elevate the excitability and discharge of dorsal horn neurons [43, 102] and to induce changes in sensory processing at the level of the spinal dorsal horn including altered calcium-dependent signal transduction mechanisms [103], a shift in anion gradient [104], microglial activation [105], decreased inhibitory mechanisms [58], apoptosis [106] and others. It is thought that this modified sensory processing at the level of the spinal dorsal horn, termed central sensitization [50, 107, 108] or long term potentiation [109], contributes to neuropathic pain by exacerbating excitatory transmission to supraspinal structures.

In view of the evidence that central sensitization in humans is maintained by a constant barrage of synaptic activity from primary afferent nerve cells [58, 110] it is important in understanding mechanisms of neuropathic pain to understand the properties of primary sensory neurons and how they adapt to or change in response to nerve injury. It is at these properties, particularly at the processes that are involved in the initial stages of neuropathology, that early pharmaceutical intervention can be aimed.

7. Standard treatment following peripheral nerve injury

For complete cut of a peripheral nerve a standard procedure is nerve repair or nerve grafting, but this approach remains suboptimal and is usually performed long after the cut has occurred. Axons have the capacity to regrow, but this is often incomplete or the regeneration misses the original tissue target. As a result there has been a wealth of research on mechanisms of regeneration and respective treatment modalities. Yet, outcome generally remains poor.

To make matters worse, leaders in the field of pain have suggested that "there is little evidence that chronic postsurgical pain can be prevented" and they cite papers such as those by Kehlet et al. [23], Gartner et al. [111] and Katz and Seltzer [112]. In fact, this assessment might just be correct, as the concept of 'prevention' of postsurgical chronic pain is usually embedded in the concept of peri-surgical anaesthesia [113-115] rather than control of the degenerative processes that lead to secondary injury to nerve cells and Schwann cells in peripheral nerves. This latter approach is not included in steps to prevent postsurgical pain, let alone a rationalized, combination therapy based on a timed sequence of pharmaceutical interventions aimed at reducing or preventing the processes involved in secondary injury to these cells. The consensus therefore teaches away from this rationalized approach toward techniques that have been proven by evidence to be relatively ineffective, condemning multiples of thousands each year to a life of unending refractory pain.

Numerous efforts have been made to develop new and effective drugs and other approaches to treat neuropathic pain. Some treatments have been found to have beneficial effects. These include treatment with multimodal analgesics [116], anticonvulsants [16, 21], botulinum toxin [117, 118], peripheral nerve electrical stimulation [119, 120], as have invasive approaches such as spinal cord stimulation [121] and administration of stem cells [122]. However, these are aimed at treating existing pain. What are not being explored are new treatments to prevent the onset of neuropathic pain or any other of the sensory, motor or autonomic adverse sequelae of peripheral nerve injury.

8. Limitations to incentives to prevent secondary injury to peripheral nerves

Trauma to peripheral nerves is not considered life threatening, whether physical, chemical, metabolic or surgical. As a result there is limited incentive to pursue medical interventions,

methods and procedures to reduce or prevent secondary peripheral nerve injury that results from trauma. For example, there is no appreciation of immediacy in medical intervention. Research on medical intervention for neuropathic pain focuses on treatment of an existing condition, once a complete diagnosis has been made. Complete or correct diagnosis can take weeks, months or even years. Standard treatment following peripheral nerve trauma typically involves drugs that reduce the pain intensity. Thus, in the pursuit of new drugs, neuropathic pain resulting from peripheral nerve trauma is becoming understood in terms of a static, or an established, condition. The processes that are involved in the initial pathophysiology of peripheral nerve injury remain poorly understood and few efforts are being made to understand or to intervene in these processes.

A second limit to incentive to understanding the pathophysiology of peripheral nerves is that a major focus of research has been on the changes in the spinal cord and other central nervous system structures that result from peripheral nerve trauma [123]. As a result, much of the research on the pathophysiology of neurons and neural support cells in neuropathic pain has focused on changes in the spinal cord, where the predominant concepts are 'central sensitization' or 'long-term potentiation' [108, 124] and 'neuroplasticity' [125], as mechanisms underlying the pain. While this is important, it has tended to shift focus away from the changes in peripheral nerves and the role of primary afferent drive in the mechanisms of neuropathic pain [27, 43, 102].

There is a rich literature pertaining to pharmacological treatments for peripheral neuropathic pain as an existing condition, summarized in a number of thorough reviews [16, 20-22, 126]. This abundant literature is largely due to the fact that neuropathic pain is a particularly debilitating type of chronic pain, yet it remains refractory to medical treatment in a large number of patients. Despite this huge medical need, there is little information or drive with regard to reducing or preventing the development of peripheral neuropathic pain, which is the focus of the present overview.

9. New approaches to minimize secondary injury following peripheral nerve injury

Despite abundant information regarding the processes and mechanisms of the changes in the periphery and in the spinal cord, there appears to be little effort being made to understand these processes and mechanisms or to develop new therapeutics to prevent trauma-induced secondary injury in peripheral nerves. Steps to reduce or to prevent the development of neuropathic pain are not generally considered in medical practice, other than steps to avoid traumatic events. Prevention, from a medical intervention standpoint, is not found in consensus statements.

Novel therapies under development retain the focus on treatment of an existing symptom. Steps to reduce or prevent secondary nerve injury following peripheral nerve trauma through immediate medical intervention do not appear in major national statements or reports, such as the US National Pain Care Policy Act of 2009, the 2011 Annual Report of the Chief Medical

Officer of the United Kingdom, or the 2011 report of the US Institute of Medicine, "Relieving Pain in America. A Blueprint for Transforming Prevention, Care, Education and Research".

Given the enormous impact of trauma-induced peripheral neuropathology and its sequelae on individuals, on families, on the healthcare system and on the economy, and the enormous social impact specifically of abuse of pain-relieving drugs, this presents an opportunity to exploit the limited knowledge we have regarding mechanisms underlying the secondary injury to peripheral nerves following traumatic events, to develop effective medical intervention to reduce or prevent the secondary processes that lead to peripheral nerve pathology.

Some insights into possible therapeutic approaches have come from animal studies, which have shown that peripheral neuropathy resulting from physical trauma is preventable when immediate and appropriate therapy is introduced [127] but is not preventable when treatment is delayed [128-131]. There is limited evidence that immediate or at least early medical intervention may have beneficial effects on long-term outcome. For example, immediate but not prolonged treatment with either an NK-1 receptor antagonist [130] or with progesterone [129] has been shown to have long-term benefit in an animal model of peripheral nerve injury. In fact, a recent study on early treatment with peripheral nerve stimulation of soldiers on the battlefield has reported improved functionality and opioid use reduction [120], a point well made as extremity trauma is a relatively more common medical condition in battle now because of advances in body armour [132].

As described above, due to the plethora of mechanisms that are triggered by event-related trauma to peripheral nerves combinatorial approach to reducing or preventing secondary injury to peripheral nerves may be necessary. There is presently no therapeutic approach to prevent or reduce the adverse health conditions or disability that result from trauma-induced damage to peripheral nerve cells, peripheral neural support cells or peripheral neural support tissues. There is little research directed at translation of new discoveries from animal studies to preventing or reducing peripheral neuropathology in humans and, as a result, until this invention there is little evidence or indication that this medical need will be met.

10. Recommendations for future research.

If new, appropriate therapeutics are to be developed in order to prevent or limit the disability that ensues from peripheral nerve injury, such therapeutics will have to target the biochemical and metabolic processes triggered by trauma, and therefore research is needed to understand these processes beyond what has been described in this overview. Further, from this understanding novel targets need to be identified that offer opportunities to develop novel therapeutics.

Injury triggers cascades of cellular, biochemical and metabolic processes, some of which tend to return nerve cells, neural support cells and neural support tissues toward normal function and cell health. Some changes tend to drive nerve cells, neural support cells and neural support tissues toward loss of cell function or cell death. The former group of processes is considered

to be restorative or adaptive processes. The latter group of processes is considered to be degenerative or maladaptive. The eventual outcome at the cellular and tissue levels is determined by or results from the balance of all the restorative and degenerative processes triggered by or resulting from the primary injury and its sequelae. Indeed, the damage caused by these secondary processes can be as serious and extensive as, or even more serious and extensive than, that caused by the primary trauma. Secondary processes also progress over time so that injury and damage can continue over the days, weeks and even months after the initial injury. Further, the secondary processes can also progress spatially so that injury and damage can spread spatially and manifest at sites remote from the site of the primary trauma to other peripheral nerves.

This balance can be tipped toward normal function and health by appropriate pharmaceutical intervention at the appropriate time. This can be achieved because of the chemical nature or basis of the restorative and degenerative processes occurring at the cellular, biochemical and metabolic levels.

As indicated above, there are many targets or points of entry for pharmaceutical promotion, facilitation or potentiation of restorative processes to tip this balance toward function and health, and there are many targets or points of entry for pharmaceutical inhibition, lessening or blocking of degenerative processes that tip this balance away from function and health toward loss of function, adverse health conditions or disability. It is recommended, then, that future research focus on understanding these mechanisms and identifying potential targets for development of new therapeutic approaches.

11. Conclusions

Conventional or standard treatment of trauma typically consists of minimizing the symptoms of the immediate, or primary, traumatic injury. With conventional or standard methods and treatments, attempts are made to minimize these immediate symptoms. Standard treatment for any persisting loss of function or disability that results from the initial trauma is typically treated by rehabilitation, which is usually initiated after there has been overt recovery from the traumatic event itself. Initiation of rehabilitation typically comes weeks or even months later, when the adverse health conditions or disability are clear and obvious.

In significant contrast, it is suggested here that in addition to standard emergency or critical care at the time of an accident or trauma specific actions be directed toward mitigating or ameliorating the sequelae of post-trauma effects that are an indirect result of a primary trauma and that are expressed as a result of the balance of restorative and degenerative processes.

Presently, there is a gap in medical care between standard practice to treat a primary injury or damage at the time of trauma, and standard practice to rehabilitate. The suggestion here is to address this gap by understanding and promoting processes that drive toward recovery and restoration of cell health and function and at the same time inhibiting processes that drive toward loss of cell function and cell death.

Significantly, the point of differentiation between conventional or standard methods and the present position is the difference between the treatment of the symptoms of the primary injury, and formulations, methods and procedures taken at or about the time of trauma to prevent or lessen damage from the secondary sequelae that may or are likely to occur.

The cascades of mechanisms leading to secondary injury are triggered within minutes to hours, yet continue to occur over the ensuing days and weeks. As a result, symptoms of secondary injury manifest over such periods, and the present position argues to reduce or prevent the manifestation or expression of these symptoms of secondary injury, which are known on the basis of incidence studies to occur.

There is a general acceptance that disability results from trauma. Incidence studies indicate that a certain number of people in a population will go on to develop disability following trauma of any given type. Medical attention has not typically been directed at reducing these numbers, or preventing them altogether. Instead, it tends to be directed at saving life and addressing the immediate condition and symptoms. Yet, much of the disability that ensues as a result of trauma is brought about by secondary injury processes, largely biochemical, which can be modified by appropriate pharmaceutical intervention. Trauma-induced disability can thus be considered an unaddressed medical need. The present position here is that the number of people who go on to develop disability following trauma can be reduced. Further, the severity of disability of those that develop a disability can be reduced. The scope and the spirit of the present overview are directed toward this unaddressed need, both by reducing the number of victims of trauma that go on to develop adverse health conditions and disability, as well as by reducing the severity of disability in those who are left with trauma-induced health conditions.

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